REMARKS/ARGUMENTS

Claims 124-126, 129-133 are pending and stand rejected in this case. The rejections to the presently pending claims are respectfully traversed.

Priority

Based on the rejections presented in the Final Office action, Applicants readdress priority. Applicants submit that they rely on the 'gene amplification' assay (Example 170), not chondrocyte redifferentiation assay for patentable utility of the instantly claimed subject matter. This utility was first disclosed in Example 23 in the U.S. Provisional Patent Application Serial No. 60/141,037, filed June 23, 1999, priority for which has been claimed in this application and relevant pages of which have been submitted to the Examiner with the previous response. (Copy enclosed). Applicants believe that they are at least entitled to an effective filing date of **June 23, 1999** based on the results of the 'gene amplification' assay for the present case.

The Examiner has indicated that the gene amplification assay was not found to be enabling as required by the 35 U.S.C. §112, first paragraph. The Examiner allegedly states that "the amplification was minimal." (Page 2 of the instant Final Office Action).

Applicants respectfully disagree and submit that the "increase in DNA" in the gene amplification assay is significant. Applicants have asserted patentable utility for the PRO1111 molecule based on the amplification of the gene encoding PRO1111. The gene encoding PRO1111 was amplified approximately 1.05-1.58 ΔCt units in seven lung tumors and 1.05-1.38 ΔCt units in four colon tumors which corresponds to $2^{1.05}$-$2^{1.58}$- fold amplification in lung and $2^{1.05}$-$2^{1.38}$- fold amplification in colon tumors respectively, or **2.0705 to 2.99 fold** in seven different lung primary tumors and **2.0705 to 2.603 fold** in four different colon primary tumors. Applicants submit that, one skilled in the art would find it more likely than not that PRO1111 is useful as a diagnostic tool for detecting certain lung or colon tumors. Additionally, the Examiner has not provided any evidence to show that such an amplification would be considered minimal by one skilled in the art.

Further, Applicants have previously submitted a Declaration by Dr. Audrey Goddard. The Declaration by Dr. Audrey Goddard provides a statement by an expert in the relevant art that "fold amplification" values of at least 2-fold are considered significant in the TaqMan™ PCR

gene amplification assay. Applicants particularly draw the Examiner's attention to page 3 of the Goddard Declaration which states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Accordingly, the **2.0705 to 2.99 fold** amplification in seven different lung primary tumors and **2.0705 to 2.603 fold** amplification in four different colon primary tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration.

The Examiner asserts that "merely because amplification may be an initial step in the formation of cancer does not equate with a substantial assertion of diagnostic utility for the encoded protein." (Page 3 of the instant Final Office Action).

In this regard, Applicants have extensively discussed throughout prosecution that amplified DNA levels are, more likely than not, associated with correspondingly increased protein levels, and submitted more than 100 references in their IDS filed on September 29, 2006 to support this position. In this statement, the Examiner seems to agree that gene amplification has diagnostic utility for the DNA, but does not for the protein. As discussed in detail in our discussions on references Orntoft *et al.*, Hyman *et al.* and Pollack *et al.*, amplified DNA levels, more likely than not, result in increased protein levels. Indeed, the totality of evidence submitted in this case should be taken into consideration. In Applicants' Response filed on September 29, 2006, Applicants argued that the evidentiary standard to be used throughout ex parte examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of

utility. The question here is whether one skilled in the art would agree that amplified DNA levels would result in increased protein levels. Applicants submit that most references in the art show that it does, and Applicants respectfully remind the Examiner that the standard is not absolute certainty. The law requires only that one skilled in the art should accept that such a correlation is more likely than not to exist. Applicants have submitted enough rebuttal evidence such that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.

It is "more likely than not" for increased mRNA levels to predict increased protein levels"

Applicants have previously submitted a twoDeclarations by Dr. Polakis (Polakis I and II). Polakis II presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (*i.e.*, greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions.

But the Examiner alleges that the two Polakis Declarations are not consistent. In particular, the Examiner alleges that in the first declaration, Dr. Polakis states that "approximately 200 gene transcripts that are present in human tumor **cells**……", while in the second declaration, he states that "approximately 200 gene transcripts that are present in human tumor **tissue**……" (Emphasis added). The Examiner also alleges that the second Declaration uses the term "at mRNA level" and "at the protein level," which is different from the first Declaration. The Examiner further alleges that it cannot determined whether these two Declarations refer to the same data set, and there has not been any explanation of why the Declarant now refers to tumor tissue rather than tumor cells, nor what the perceived significance of this change is." (Page 5 of the instant Final Office Action).

Applicants respectfully disagree and fail to see how the two Declarations are inconsistent and why the Examiner requires that the two declarations use the exact same wording. If a

mRNA/protein correlation exists in tumor cells, most likely it will exist in tumor tissues. With respect to the use of the term "overexpression at mRNA level" and "overexpression at the protein level." Applicants submit that they are simply the rephrase of "increases in the level of a particular mRNA" and "increase in the level of a particular protein." Thus, contrary to the Examiner's allegation, the two Declarations are consistent.

Applicants further submit that Polakis II does not need to provide any data specific for PRO1111 because the data in Polakis II was provided as a proof of existence of a general correlation (more likely than not) between mRNA and protein expression for any given gene. Applicants are not required either under the law or under the Utility Guideline to prove that there is "absolute certainty" that mRNA/protein correlation exists. Therefore, in order to establish utility, Applicants is not required to provide any specific information for PRO1111.

Further, Applicants would like to bring to the Examiner's attention a recent decision by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that "there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." (Page 9 of the Decision). Applicants submit that, in the instant application, the Examiner has likewise not presented any evidence specific to the PRO1111 polypeptide to refute Applicants' assertion of a correlation between mRNA levels and protein expression. Accordingly, Applicants respectfully request that the outstanding rejections be withdrawn and this case passed to issue.

Applicants believe that, due to an error, the Examiner states "the Polakis II Declaration is not sufficient to overcome the rejection of Claims 58-62 under 35 U.S.C. §101 and §112, second paragraph." (Page 5 of the instant Final Office Action).

Claims 58-62 are not pending in this application. Applying this rejection to pending Claims 124-126, 129-133, Applicants submit that, based on the discussions presented above regarding the Polakis Declarations, the gene amplification assay presented in Example 170 of the specification is sufficient to establish a specific and substantial utility at least for the polypeptide of SEQ ID NO:228.

In considering the evidence that there is a positive correlation between changes in mRNA levels and changes in the corresponding protein levels, the Examiner has asserted that Molecular

Biology of the Cell (Alberts) acknowledges that "other controls can act later in the pathway from RNA to protein to modulate the amount of protein that is made." (Page 6 of the instant Final Office Action). The Examiner has further asserted that Genes VI (Lewin) acknowledges that "initiation of transcription...is not the only means of regulating gene expression." (Page 6 of the instant Final Office Action).

Applicants **do not need** to establish that transcription initiation is **the only means** of regulating gene expression in order to meet the utility standard. Instead, as long as it is the most common point of regulation, as admitted by the Examiner, it would be more likely than not that a change in the transcription level of a gene gives rise to a change in translation level of a gene. Applicants note that both Alberts and Lewin make clear that it is far more likely than not that protein levels for any given gene are regulated at the transcriptional level. Alberts, for example, states that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379. (Emphasis added). In a similar vein, Lewin states that "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848. (Emphasis added). Thus, the utility standard is met.

With respect to Applicants' arguments regarding Meric *et al.*, the Examiner asserts that Meric teaches that "gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability." (Page 6of the instant Final Office Action).

Applicants respectfully submit that Meric simply summarizes the translational regulation of cancer cells. Meric indicates that translation initiation is regulated in response to nutrient availability and mitogenic stimulation and is coupled to cell cycle progression and cell growth. Meric further discusses how alterations in translation control occur in cancer. For example, variant mRNA sequences can alter the translational efficiency of individual mRNA molecules. (See Abstract). Meric further teaches that the changes in translational efficiency of a mRNA transcript depend on the mutation of a specific mRNA sequence. (Page 973, column 2 to page 974, column 1). Meric never suggests that the translation of a cancer gene is suppressed in cancer in general, and that therefore, increased mRNA levels will not, in general, yield increased

protein levels. To the contrary, Meric teaches that the translation efficiency of a number of cancer genes is enhanced in cancer cells compared to their normal counterparts. For instance, in patients with multiple myeloma, a C-T mutation in the c-myc IRES was identified and found to cause an enhanced initiation of translation. (Page 974, column 1). Therefore, the level of proteins encoded by these genes increases in cancer cells at an even higher magnitude than the corresponding mRNA level. Thus, Meric clearly supports Applicants' assertions that it is more likely than not that, in general, changes in mRNA levels are correlated with changes in protein levels.

The Examiner has further asserted that "applicants have found a single nucleic acid, SEQ ID NO:228, that is found to be aneuploid in a small number of tumor cell lines." (Page 9 of the instant Final Office Action). Further the Examiner states that "the most parsimonious explanation is aneuploidy, with no evidence that he chromosome bearing PRO1111 was preferentially amplified(as apposed to other chromosomes). (Pages 2-3 of the instant Final Office Action).

First of all, the Examiner does not provide any evidence for her assertion that the gene amplification in this instance is due to aneuploidy. Even if it were, Applicants submit that it is known in the art that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes or from chromosomal aneuploidy. As explained by Dr. Ashkenazi in his Declaration (submitted with Applicants' Amendment and Response filed on November 8, 2004),

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Applicants submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is useful as a diagnostic marker.

Moreover, it appears that the Examiner's concern is with regard to the underlying mechanism of gene amplification, and not with the positive results themselves. However, the Examiner's concerns regarding the mechanism of PRO1111 gene amplification associated with

any type of cancer versus normal tissue, should in no way negate the utility of the claimed invention. The fact remains that the gene amplification results demonstrate overexpression of PRO1111 in the named tumor. One of ordinary skilled in the art does not need to know the underlying mechanism of the overexpression of PRO1111, whether aneuploidy, mutation or translocation, to practice the claimed invention. One of ordinary skill in the art, in possession of these results, would have believed it more likely than not that the PRO1111 polypeptides are useful for their asserted utility. Therefore, this rejection is not proper.

The Examiner further asserts that Godbout *et al.* teaches that "it is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell." (Page 7 of the instant Final Office Action).

Applicants respectfully submit that the passage cited by the Examiner is based upon two references from 1987 and 1992. In contrast, Applicants have already made of record three more recent references published in 2002 by Ornfoft *et al.*, and Pollack *et al.*, which collectively teach that in general, mRNA expression increases protein expression. Applicants submit that these more recent references must be acknowledged as more accurately reflecting the state of the art regarding the correlation between mRNA expression and protein expression than the references cited by Godbout *et al.*

The Examiner further states that, "the Examiner cannot find any reason to suspect, that the protein encoded by the PRO1111 gene would confer such a selective advantage to a cancerous cell, and found none." (Page 7 of the instant Final Office Action).

In this rejection, the Examiner further contemplates an explanation for how PRO1111 confers selective advantages to the tumor cell, in other words, on the mechanism by which PRO1111 acts. That is, rather than focusing on the positive result itself, the Examiner seems to focus on the mechanism of action.

However, knowledge of the mechanism is not relevant or required for the claimed invention to be useful. In fact, as stated by the Federal Circuit, "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." In re Cortwright, 165 F.2d 1353, 1359 (Fed. Cir. 1999). The Federal Circuit has also stated that "[a]n invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only

limited utility and is not operable in certain applications is not grounds for finding lack of utility." Envirotech Corp. v. Al George, Inc. 730 F.2d 753,762, 221 USPQ 473,480 (Fed. Cir. 1984)."

More importantly, Applicants submit that the cited reference Godbout *et al.,* was presented as evidence to support the existence of a general correlation between mRNA expression and protein expression. Applicants have asserted utility for PRO1111 as a novel tumor marker based on its positive result in the gene amplification assay. Furthermore, Appellants note that selective advantage to cell survival may not be the only mechanism by which genes impact cancer. As the Examiner is aware, there are many pathways to tumorigenesis, and screening for novel diagnostic tumor markers is routine in the art. For this additional reason, the Examiner's concerns are misplaced. This heightened requirement of a showing of mechanism imposed by the Examiner is improper according to the Utility standards set by the USPTO.

Applicants respectfully submit that, as discussed in the previously filed Preliminary Amendment and in the instant Response, none of the references cited by the Examiner suffices to establish a lack of general correlation between changes in mRNA expression of a gene and changes in its corresponding protein expression level. On the other hand, Applicants have provided an overwhelming amount of evidences supporting the existence of a mRNA expression/protein correlation. Accordingly, the evidences of the record have already established that it is "more likely than not" that increased mRNA expression predict increased protein levels.

Li *et al.*

The Examiner has cited Li *et al.* as teaching that "68.8% of the genes showing over-representation in the genome did not show elevated transcript levels." (Page 8 of the instant Final Office Action).

Applicants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression. The authors note that "[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma." (Page 2629, col. 1). In fact, as

explained in the Supplemental Information accompanying the Li article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. As discussed in Applicants' previous Responses, and in the Goddard Declaration of record, an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0. As discussed above the PRO1111 gene showed 2.0705 to 2.99 fold amplification in seven different lung primary tumors and 2.0705 to 2.603 fold amplification in four different colon primary tumors, thus meeting this standard. It is not surprising that, by using a substantially lower threshold for considering a gene to be amplified, Li *et al.* would have identified a number of genes that were not in fact significantly amplified, and therefore did not show any corresponding increase in mRNA expression. The results of Li *et al.* therefore do not disprove that a gene with a substantially higher level of gene amplification, such as PRO1111, would be expected to show a corresponding increase in transcript expression.

Applicants have clearly demonstrated a credible, specific and substantial asserted utility for the PRO1111 polypeptides, for example, as a diagnostic marker for lung or colon tumors. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides.

Therefore, the rejections under 35 U.S.C. §101 and §112 of Claims 124-126 and 129-133 should be withdrawn.

Claim Rejections – 35 U.S.C. §112, First Paragraph - Enablement

Claims 132-133 are rejected under 35 U.S.C. §112, first paragraph, because allegedly "the specification, while being enabling for the protein of SEQ ID NO:229 or fragments thereof for making antibodies or having chondrocyte redifferentiation activity, does not reasonably provide enablement for proteins that are encoded by a nucleic acid that is amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon." (Page 9 of the instant Final Office Action).

Applicants respectfully disagree.

Applicants submit that they rely on the 'gene amplification' assay (Example 170) not chondrocyte redifferentiation assay for patentable utility of the instantly claimed subject matter. The teachings of the specification should be evaluated through the eyes of one skilled in the

pertinent art at the effective filing date of **June 23, 1999** of the present application. As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."[1] As discussed above, a considerable amount of experimentation is permissible, if it is merely routine.

Claims 132-133 recite "native polypeptide sequences" with the functional recitation "wherein the nucleic acid encoding said polypeptide is amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon." By following the disclosure in the specification, particularly the gene amplification assay of Example 170, one skilled in the art could easily test whether a variant PRO1111 polypeptide was amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon. Those variants whose encoding nucleic acids are not amplified in lung tumors are not encompassed by the claims. Applicants further submit that the claims recite native sequence polypeptide variants. It is understood that many polypeptides and especially tumor antigens are known to have different isoforms or variants[2]. One of skill in the art would therefore reasonably expect there to be variants of PRO1111 that are also amplified in lung or colon tumors. The specification has provided detailed protocols for the gene amplification assay, in Example 170, such that one of ordinary skill in the art could identify those variants meeting the limitations of the claims, without any undue experimentation. Applicants claim only those variants which meet both recitations of the claims. Thus, these recitations clearly act to further define the claimed genus of Claims 132 and 133.

The specification further describes methods for the determination of percent identity between two amino acid sequences. (See page 306, line 14, to page 308, line 6). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to

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[1] M.P.E.P. §2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

[2] Peng *et al.*, *Cancer Research*, 64:8911-8918 (2004); Kiss *et al.*, *Anticancer Research* 24:3965-3970 (2004); Perego *et al.*, *Molecular Carcinogenesis* 42(4):229-239 (2005); Nagao *et*

changes that may be made to a PRO polypeptide without adversely affecting its activity. (Page 371, line 6, to page 373, line 17). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids. (Table 6, page 372). Accordingly, one of skill in the art would be able to identify whether a variant PRO1111 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 371, line 6, to page 375, line 9) and methods of preparing the PRO polypeptides. (See page 375, line 11 and onward).

Therefore, Applicants respectfully submit that the specification provides ample guidance such that one of skill in the art could readily test a variant polypeptide. This biological activity together with the well defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, sufficiently defines the claimed genus such that, one skilled in the art, at the effective date of the present application, would have known how to make and use the claimed polypeptide sequences without undue experimentation.

Hence Applicants respectfully request reconsideration and reversal of the enablement rejection of Claims 132-133 under 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 U.S.C. §112, First Paragraph - Written Description

Claims 132-133 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing. (Page 10 of the instant Final Office Action).

Applicants respectfully disagree.

Applicants further submit that, whether a specification shows that Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teachings provided by the specification. The inventor is

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al., Genomics 85:462-471 (2005); Hong *et al., Cancer Research* 64:5504-5510 (2004) (previously submitted).

not required to describe every single detail of his invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

Claims 132-133 recite the functional recitation "wherein the nucleic acid encoding said polypeptide is amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon." Arguments for patentable utility based on the gene amplification assay have been presented above. The present invention is from the field of recombinant DNA technology. It is well established that the level of skill in this field is relatively high, and is represented by a Ph.D. scientist having several years of experience in the pertinent field. Accordingly, the teachings imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

Applicants submit that the instant specification satisfies the Written Description Guidelines issued by the U.S. Patent Office since the specification provides detailed description about the cloning of variants and provides step-by-step guidelines and protocols for the gene amplification assay for testing nucleic acids in a PCR based assay at least in Example 170. Further, as discussed above under enablement, the specification further describes methods for the determination of percent identity between two amino acid sequences. (See page 306, line 14, to page 308, line 6). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity. (Page 371, line 6, to page 373, line 17). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 372). Accordingly, by following the disclosure in the specification, one of skill in the art would be able to identify whether a variant PRO1111 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 371, line 6, to page 375, line 9) and methods of preparing the PRO polypeptides. (See page 375, line 11 and onward).

The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids. Accordingly, a description of the claimed genus has been achieved. Applicants submit that the genus of nucleic acids that code for the polypeptide of SEQ ID NO:229 with 95% similarity and further, which possess the functional property that it is

"wherein the nucleic acid encoding said polypeptide is amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon" would encompass a genus that meets the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description. Hence, Applicants request that the present rejection be reconsidered and reversal of the written description rejection of Claims 132-133 under 35 U.S.C. §112, first paragraph.

Claim Rejections – 35 U.S.C. §112, Second Paragraph

Claims 132-133 are rejected under 35 U.S.C. §112, second paragraph, for allegedly "being indefinite." (Page 11 of the instant Final Office Action). The Examiner contends that "the metes and bounds of proteins encoded by the nucleic acids 'amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon'...cannot be determined." (Page 11-12 of the instant Final Office Action).

Applicants respectfully disagree. As discussed above under the Enablement and Written description issues, Applicants submit that the instant specification provides detailed description for identifying the genus of nucleic acids that code for the polypeptide of SEQ ID NO:229 with 95% similarity and further, which possess the functional property that it is "wherein the nucleic acid encoding said polypeptide is amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon." It also provides step-by-step guidelines and protocols for testing these DNA in the gene amplification assay, a PCR based assay at least in Example 170. Accordingly, the metes and bounds of proteins encoded by such nucleic acids are clearly defined such that one skilled in the art would know how to make the invention. Applicants respectfully request that the present rejection be reconsidered and reversal of the rejection of Claims 132-133 under 35 U.S.C. §112, second paragraph.

Claim Rejections – 35 U.S.C. §102

1. Claims 124-126, 129 and 132-133 are rejected under 35 U.S.C. §102(a) allegedly as being anticipated by Wang *et al.* (Genbank Accession No. AF196976; pub 10/20/1999). (Pages 13-14 of the instant Final Office Action).

Applicants submit that they rely on the 'gene amplification' assay (Example 170) for patentable utility of the instantly claimed subject matter. This utility was first disclosed in

Example 23 in the U.S. Provisional Patent Application Serial No. 60/141,037, filed June 23, 1999, priority for which has been claimed in this application and relevant pages of which have been submitted to the Examiner with the previous response. (Copy enclosed). Applicants are at least entitled to an effective filing date of **June 23, 1999** based on the results of the 'gene amplification' assay for the currently pending claims, and this date precedes the publication date for Wang *et al.* Therefore, Wang *et al.* is not prior art under 35 U.S.C. §102(a), and hence this rejection should be withdrawn.

2. Claims 119-123 and 130-133 are rejected under 35 U.S.C. §102(a) allegedly as being anticipated by Jacobs *et al.* (Genbank Accession No. AAY28806; pub: October 7, 1999) (Page 14 of the instant Final Office Action).

Claims 119-123 have been canceled in the previously filed Amendment and Response on September 29, 2006, hence this rejection is moot for these claims. Further, as discussed above, Applicants are at least entitled to an effective filing date of **June 23, 1999** based on the results of the 'gene amplification' assay for the currently pending claims, and this date precedes the publication date for Jacobs *et al.* Therefore, Jacobs *et al.,* is not prior art under 35 U.S.C. §102(a) and hence this rejection should be withdrawn.

3. Claims 130-133 are rejected under 35 U.S.C. §102(a) allegedly as being anticipated by Jacobs *et al.* (WO 99/50405, pub date 10/7/99). Further, the Examiner states that "The reference is silent with respect to whether or not the nucleic acid encodes a protein with chondrocyte redifferentiation activity." (Page 14 of the instant Final Office Action).

Applicants submit that they rely on the 'gene amplification' assay (Example 170) not chondrocyte redifferentiation assay for patentable utility of the instantly claimed subject matter. For the reasons discussed above, Applicants are at least entitled to an effective filing date of **June 23, 1999** based on the results of the 'gene amplification' assay for the currently pending claims, and this date precedes the publication date for Jacobs *et al.* Therefore, Jacobs *et al.,* is not prior art under 35 U.S.C. §102(a) and hence this rejection should be withdrawn.

4. Claims 124, 127 and 130-133 are rejected under 35 U.S.C. §102(e) allegedly as being anticipated by Shimkets *et al.* (U.S. Patent No. 6,689,866 dated 3/8/00). (Page 14 of the instant Final Office Action).

For the reasons discussed above, Applicants are at least entitled to an effective filing date of **June 23, 1999** based on the results of the 'gene amplification' assay for the currently pending claims. Shimkets *et al.* is dated after the effective filing date of **June 23, 1999.** Therefore, Shimkets *et al.* is not prior art and these rejections should be withdrawn.

Claim Rejections – 35 U.S.C. §103(a)

1) Claims 130 and 132-133 are rejected under 35 U.S.C. §103(a) allegedly as being obvious over any one loci AI769814, AI435407, AI470931 or T15752 in view of Sibson *et al.* (Page 16 of the instant Final Office Action).

The Examiner relies on the sequence comparison analysis summarized in the table on Page 12 of the instant Final Office Action to assert AI769814, AI435407, AI470931 or T15752 as prior art. For the reasons discussed below, Applicants believe that AI769814, AI435407, AI470931 or T15752 is not prior art.

Applicants respectfully remind the Examiner that the instant case is directed to **polypeptides**, particularly, to the polypeptide of SEQ ID NO:229, and not to nucleic acids. Applicants note that the polypeptide sequences encoded by AI769814, AI435407, AI470931 or T15752 were not reduced to practice in the cited art nor did the art provide any disclosure whatsoever of the full-length polypeptide encoded by any of these nucleic acid fragments. Hence, this rejection for the instant polypeptide case based on nucleic acid ESTs alone is not appropriate and therefore, AI769814, AI435407, AI470931 or T15752 are not prior art.

Applicants would like to point out that locus AI769814 has a publication date of December 21, 1999. For the reasons discussed above, Applicants are at least entitled to an effective filing date of **June 23, 1999** based on the results of the 'gene amplification' assay for the currently pending claims. Locus AI769814 is dated after the effective filing date of **June 23, 1999.** Therefore, Locus AI769814 is not prior art and these rejections should be withdrawn.

The Examiner alleges that: 1) Locus AI769814 has 100% identity to bases 1703-2180 of SEQ ID NO:228; 2) Locus AI435407 has 99.8% identity to bases 1743-2185 of SEQ ID NO:228; 3) Locus AI470931 has 100% identity to bases 1795-2179 of SEQ ID NO:228; 4) Locus AI769814 has 100% identity to bases 1703-2180 of SEQ ID NO:228; and 5) Locus T15752 has

100% identity to bases 1870-2184 of SEQ ID NO:228. (Page 12 of the instant Final Office Action).

Initially, Applicants note that the Examiner did not enclose the alignments of AI769814, AI435407, AI470931 or T15752 and the instantly claimed SEQ ID NO:228, with the instant Final Office Action.

The Examiner states that "sequence identity is calculated relative to the shorter of the two sequences being compared." (Page 16 of the instant Final Office Action).

Applicants strongly disagree with the Examiner's calculation of sequence similarity because sequence similarity should be calculated by following the definition(s) provided in the specification for comparison of sequences, not the Examiner's definition. Indeed, the specification describes methods for the determination of percent identity between two nucleic acid sequences. (See page 309 to page 310, copy enclosed). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention.

The example shown in Tables 5 (Page 337 of the Specification, copy enclosed) scenarios wherein the number of identical nucleotides in a nucleic acid sequence that is being compared to is shorter than the full-length of the PRO-DNA nucleic acid sequence.

Applicants submit the sequence alignment comparing instantly claimed Sequence 1 (the instant applications' SEQ ID NO:228 sequence) with Sequence 2 (AI769814, AI435407, AI470931 or T15752). (See Alignments enclosed).

AI769814

Applicants analysis of the sequence alignment comparing the instantly claimed Sequence 1 (the instant applications' SEQ ID NO:228 sequence) with Sequence 2 (AI769814) results in 478 identical nucleotides out of the total 2185 nucleotides. (See Alignment I enclosed).

AI435407

Applicants analysis of the sequence alignment comparing the instantly claimed Sequence 1 (the instant applications' SEQ ID NO:228 sequence) with Sequence 2 (AI435407) results in 441 identical nucleotides out of the total 2185 nucleotides. (See Alignment II enclosed).

AI470931

Applicants analysis of the sequence alignment comparing the instantly claimed Sequence 1 (the instant applications' SEQ ID NO:228 sequence) with Sequence 2 (AI470931) results in 385 identical nucleotides out of the total 2185 nucleotides. (See Alignment III enclosed).

T15752

Applicants analysis of the sequence alignment comparing the instantly claimed Sequence 1 (the instant applications' SEQ ID NO:228 sequence) with Sequence 2 (AI769814) results in 359 identical nucleotides out of the total 2185 nucleotides. (See Alignment IV enclosed).

Based on the teachings and the clearly disclosed definition of the specification, Applicants respectfully submit that the correct percent identity comparing the AI769814 locus with the instant applications' SEQ ID NO:228 should be calculated as follows:

> (number of matching nucleotides between the two nucleic acid sequence) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) = (478 divided by 2185) times 100 = **21.87%** (see alignment enclosed)
>
> Based on the above calculations, the correct percent identity comparing the loci AI435407, AI470931 and T15752 with the instant applications' SEQ ID NO:228 results in **20.18%, 17.62% and 16.15%** respectively. (see alignments enclosed)

That is, when calculating the nucleic acid sequence identity with any portion of the AI769814, AI435407, AI470931 and T15752, the full-length of SEQ ID NO:228 must be used in the denominator which only results in 21.87%, 20.18%, 17.62% and 16.15% identities.

Applicants have submitted the above alignments and sequence identity analysis for the Examiner's review eventhought the instant case is directed to **polypeptides**, particularly, to the polypeptide of SEQ ID NO:229, and not to nucleic acids.

The loci AI769814, AI435407, AI470931 and T15752 disclose a sequence that is 21.87%, 20.18%, 17.62% and 16.15% identical to SEQ ID NO:228.

As discussed above, loci AI769814, AI435407, AI470931 and T15752 does not disclose each and every limitation of Claims 130 and 132-133. Further, Sibson *et al.*, does not cure the deficiencies of loci AI769814, AI435407, AI470931 and T15752. Since the primary reference

falls as a prior art reference, Applicants respectfully submit that the instant claims are not obvious over loci AI769814, AI435407, AI470931 and T15752 in view of Sibson *et al.*

2) Claim 131 is rejected under 35 U.S.C. §103(a) allegedly as being obvious over any one loci AI769814, AI435407, AI470931 or T15752 in view of Sibson *et al.* and further in view of U.S. Patent No. 5,116,964 (Capon). (Page 17 of the instant Final Office Action).

As discussed above, loci AI769814, AI435407, AI470931 and T15752 does not disclose each and every limitation of Claims 131. Further, Sibson *et al.*, and Capon *et al.*, does not cure the deficiencies of loci AI769814, AI435407, AI470931 and T15752. Since the primary reference falls as a prior art reference, Applicants respectfully submit that the instant claims are not obvious over loci AI769814, AI435407, AI470931 and T15752 in view of Sibson *et al.*, and Capon *et al.*

3) Claims 130 and 131 are rejected under 35 U.S.C. §103(a) allegedly as being obvious over Wang *et al.,* Genbank Accession No. AF196976 in view of Sibson *et al.*, and Capon *et al.,* U.S. Patent No. 5,116,964. (Pages 17-18 of the instant Final Office Action).

For the reasons discussed above, Applicants are at least entitled to an effective filing date of **June 23, 1999** based on the results of the 'gene amplification' assay for the currently pending claims, and this date precedes the publication date for Wang *et al.* Therefore, Wang *et al.* is not prior art. Since the primary reference falls as a prior art reference, Applicants respectfully submit that the instant claims are not obvious over Wang *et al.*, in view of Sibson *et al.*, and Capon *et al.*

Accordingly, withdrawal of the rejection of Claims 130, 131 and 132-133 under 35 U.S.C. §103(a) is respectfully requested.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C17**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: January 18, 2008

By:_____
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